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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,152	06/15/2001	Giulia Kennedy	097268061663.002	8227

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,152	KENNEDY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-50 and 56-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50 and 56-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 4/5/2004 have been entered. Claims 1-42 and 51-55 are cancelled and claims 43-45 and 50 are amended. Claims 43-50 and 56-59 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 43-50 and 56-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte*

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 43-50 and 56-59 are broadly drawn to a method for detecting a cancerous cell comprising detecting a level of a nucleic acid gene product in a test cell, wherein said gene is identified by the sequence of SEQ ID NO:3, or complement thereof; and comparing the level of said nucleic acid gene product to a control level of said nucleic acid gene product. The specification does not at all enable correlating the level of SEQ ID NO: 3 with the detection of a colon cancer cell or a cancerous cell generally. The specification does not specify any examples of such well-established, *in–vitro* model systems, practiced methods or evidence for the ability of the detected expression of SEQ ID NO:3 to be correlated with the presence of any sort of cancerous cell. The examples that are taught in the specification include polynucleotides that correspond to genes differentially expressed in colon tissue from a **single** patient(Table 3). Table 3 teaches that Cluster 9083, including SEQ ID NO:3, as well as many other partial mRNA transcripts, is over-expressed ten times in Tumor(lib16) clones and 14 times greater in High Met(lib17) clones than in the normal (lib 15) clones. The table does not teach that SEQ ID NO:3 **alone** is over-expressed consistently in an adequate sample size representing more than just a single, isolated patient. Table 4 of the specification teaches the cluster 9083, including SEQ ID NO: 3 as well as many other partial mRNA transcripts to have a "strong" similarity to Ankyrin repeats. The specification does not teach which specific partial mRNA transcript in the cluster actually shares the similarity nor does the specification teach the relevance that such similarity has to the detection of any sort of cancerous cell. In example 4, page 84, the specification teaches that cluster 9083(SK2) is over-expressed in 3 out of 4 patients, designated as "UC#1,

UC#2, UC#4, and UC#7." However, the specification omits an explanation of to what each "UC#" designation corresponds. In Table 1, UC#2 is defined as both a normal colon and tumor colon cDNA library, it is therefore not clear to which cDNA library Example 4 is referring. In addition, the table does not make reference to any of UC #1, 4, or 7. Furthermore, although Table 1 reveals SEQ ID NO:3, cluster 9083, and SK2 in the same row of the table, the specification omits any explanation of how each entity is related to one another and as a result, the specification does not teach the relevance of the Example 4 results with respect to SEQ ID NO:3. Tables 5 and 6 totally omit any teaching of SEQ ID NO: 3 and correlating its level of expression with the detection of a colon cancer cell or cancerous cells generally. It is highly unpredictable to extrapolate findings from any of the specification's teaching to a method for detecting a cancerous cell comprising detecting a level of a nucleic acid gene product in a test cell obtained from a cell of a subject, wherein said gene is identified by the sequence of SEQ ID NO:3, or complement thereof; and comparing the level of said nucleic acid gene product to a control level of said nucleic acid gene product. It is important to note that even if applicant would enable the detection of cluster 9083 in cancerous cells, the same detection of SEQ ID NO: 3 would not be enabled for determining cancerous cells. Furthermore, while even if the method's step of identifying that SEQ ID NO: 3 is over expressed in cancerous cells, which characterizes the "how to make" portion of the enablement requirement, is enabled, the specification still omits teachings to enable the "how to use portion" as any teachings of how to use the discovered over-expressed SEQ ID NO:3 once it has been discovered.

With respect to claims 56-59 drawn to a method for assessing tumor burden by the detection of an over-expressed SEQ ID NO:3 in a colon tissue sample. The specification does not teach what

characterizes tumor burden, and in addition to not teaching the overexpression of SEQ ID NO:3 as stated supra, does not teach how an over-expression of SEQ ID NO:3 would relate to tumor burden. As a result, once again, neither prong of the enablement requirement is taught by the specification. The nature of this invention is quite unpredictable because it requires a reliance on the prophetic testimony by applicant that the detection of a larger, nebulously defined group, including SEQ ID NO:3, cluster 9083, enables the above methods for detecting cancerous cells or colon cancer cells through the detection of SEQ ID NO:3. In the same way, the method for assessing tumor burden remains not enabled.

Scope of the invention. The scope of the invention is very broad, claiming methods for detecting any cancerous cell comprising a method of detecting any level of any nucleic acid gene product identified by SEQ ID NO:3 and comparing the detected levels to that of a control level of the gene product. Much unpredictability exists in the broad claiming of this method including such general limitations as "detecting a level" and comparing this level to a "control level". Furthermore, as alluded to in the Nature of the invention, even if applicants would enable detection of an over-expressed SEQ ID NO:3, they would still be required to enable the connection to colon cancer and the ability to asses tumor burden.

State of the art. The prior art does not disclose a method for detecting a cancerous cell comprising detecting a level of a nucleic acid gene product in a test cell obtained from a cell of a subject, wherein said gene is identified by the sequence of SEQ ID NO:3, or complement thereof; and comparing the level of said nucleic acid gene product to a control level of said nucleic acid gene product, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art in the reliability of extrapolating data from a

detection involving a single patient to reflect a general trend for all detection(As seen in Table 3) and the prior art's lack of support for results that have been obtained through cell lines to necessarily reflect the same results that would occur in vivo(Table 1) results in the invention being unpredictable in terms of its use as presently claimed. First, with respect to the use of a single patient's data as proof of a general trend, the art teaches that a large sample size representing a variation of constituents is required for obtaining accurate results. Falzarano et al teach a method of screening for colon cancer in which, "utilizing the large sample size" was an important component in their study's objectives(Hawaii Med J., 2002). In addition, the National Cancer Institute teaches that "a trial designed to correct for or eliminate selection and other biases... would require a large sample size"(Cancer Prevention, 2002). Furthermore, with respect to the extrapolation of data from cell lines, it is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur in vivo (see, for example, Dermer et al (BioTechnology (1994) 12: 320). Both, the use of a single patient to determine a general trend and the extrapolation of data obtained from cell lines to in-vivo approaches, makes drawing conclusions about the present data highly unpredictable.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning single patient studies, entire clusters of data, cell lines, cDNA libraries of unknown origin and SEQ ID NOS. Considering the unpredictability surrounding the extrapolation of data from experiments using such different compositions as a cluster of many partial mRNA transcripts, individual mRNA transcripts, cDNA libraries, and single sample studies, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and

unpredictable trial and error experimentation in order to practice the invention by detecting the expression level of SEQ ID NO:3. In addition, considering the lack of working examples showing the association between a particular expression level of SEQ ID NO:3 alone and any type of cancerous cell, even more unpredictability exists.

Level of skill in the art. The level of skill involved in relating characteristics of such different molecules and compositions(cluster 9083, cDNA libraries and SEQ ID NO:3 etc) to each other is very high if not impossible. Additionally, the functional use of such assumed similar properties from such different molecules is seen, in this instance, to be prophetic.

Unpredictability of the art. There are examples of why the study parameters used in the present application can lead to great unpredictability in the art as illustrated in the State of the Art section. Both the prior art and the instant specification are deficient in terms of teaching the applicability of cluster data and data relying solely upon a single patient to that of SEQ ID NO:3 expression. Furthermore, the lack of teachings of how to use the expression or putative over-expression of SEQ ID NO:3 to identify cancerous cells, colon cancer cells or to asses tumor burden all contribute to the great unpredictability involved in making and using this invention. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Response to Arguments:

Applicant's arguments filed 4/5/2004 have been fully considered but they are not persuasive. Applicants respectfully submit that "SEQ ID NO:3" "SK2", "CHIR-8", "Candidate ID 181" and "CLUSTER 9083" refer to the same gene: a gene that encodes the nucleotide sequence of SEQ ID NO:3. While it is possible that "CLUSTER 9083" may be inclusive of "SEQ ID NO:3", it is not clear from the specification that they are analogous terms. In fact, the specification(see paragraph [00219]) teaches that a cluster is a "group of clones". While applicant argues that CLUSTER 9083 is the same as SEQ ID NO:3, there is no evidence of record in the specification as originally filed to support this conclusion. It is therefore unpredictable to assume that the overexpression of an entire cluster, not just of SEQ ID NO:3, enables the method with respect to only SEQ ID NO:3. It is not clear what other sequences 9083 includes in addition to SEQ ID NO:3. While applicant's inclusion of Tables 2 and 3, and associated arguments are acknowledged, it remains unpredictable to correlate the overexpression of the many sequences of "CLUSTER 9083" necessarily with one of the cluster's sequences. With respect to applicant's comments regarding Table 1 the applicant is reminded that this table makes unclear the actual characteristics had by the patient "UC#2" as it is referred to in three different ways in this table (i.e. Table 1 uses "UC#2" to describe a normal patient's colon, a patient with a tumorous colon and a patient with liver metastasis from colon tumor). Furthermore, there is no description in Table 1of UC #1, UC #4, or UC #7. As a result, it is unclear on page 84 to which of the three patients the UC#2 sample belongs and furthermore to what patient population UC #1, UC #4, and UC #7 belong in this table detailing cluster #9083 over-expression on page 84 of the specification. This table is even further deficient considering the lack of any guidance as to what amount of a difference in expression is deemed by applicant

to be significantly "over-expressed"(i.e. UC#4's PT sample is only .0001 more expressed than the normal). Applicant argues that SEQ ID NO: 3 is "significantly upregulated" in 75% of the patients in this table. It is not clear how .0001 is being considered to be a "significantly up-regulated" amount. Furthermore, in UC#1, the PT sample is under-expressed as compared to the normal sample. The examiner is not able to understand applicant's data as currently assembled in this particular table. Additionally, a p-value or another means to show statistical significance is absent and as a result the figure does not prove to be informative. Furthermore, the applicant should note that the examiner's inclusion of the Falzarano and NCI references was meant only to teach a general principle recognized by practioner's of various different subject matters, that a large sample size is an important component in research studies. The same is true for the Dermer et al. reference and its teaching that cell line data extrapolation is generally an unpredictable arena. In addition, applicant asserts that the "claims only recite that if the gene identified by SEQ ID NO:3 is differentially expressed relative to a control level, such is indicative that the cell is cancerous"(Pg. 7 of response), and further that "one of skill in the art would recognize that expression of the gene identified by SEQ ID NO:3 is significantly up-regulated in many, if not most or all, colon cancers". However, the applicant should note that the examiner is interpreting their claim as a method for detecting any cancerous cell by detecting any level of SEQ ID NO: 3 in any test cell and as such the claims include detecting any type of cancerous cell. It should also be noted that results obtained with one type of cancer cannot be extrapolated to all types of cancers(data for only colon cancer present in some cases). As a result, the method is not enabled by the specification as originally filed for the reasons made of record above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

6/8/2004

CARLA J. MYERS
PRIMARY EXAMINER